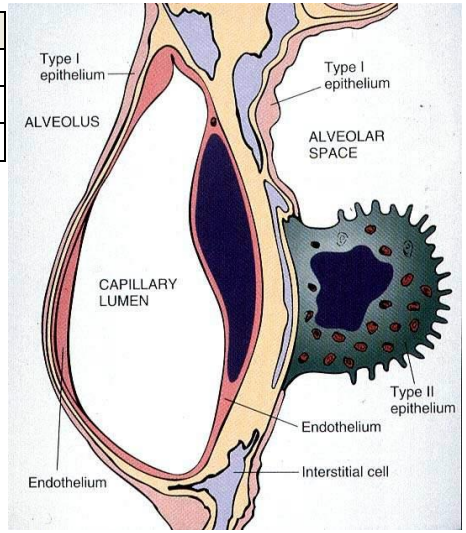
Pulmonary System

HbMutation	Shift	Genetic shift
Hb Kansas	Right shift to 70-75mmHg	Glutamate->Valine, Beta 76
Hb Montefiore	Left shift to 19.4	Aspartate->Tyrosine, Alpha 126
Hb Ohio	Left shift to 16.8	Alanine->Aspartate, Beta 142

I Physiology/Pathology



The right lung has 3 lobes, shorter bronchus at a 155 degree angle (most likely to aspirate). The left lung has two lobes and a longer bronchus at a 135 degree angle. The conducting portions (dead space volume V_D) has psuedostratified, columnar, ciliated epithelium with submucosal glands. The glands are lost first and then the terminal bronchioles lack cilia (these cells are called Clara cells).

The acinus is the respiratory portion of the lungs (respiratory bronchioles, alveolar ducts, alveolar sack, alveoli. A respiratory lobule includes 3-5 terminal bronchioles and their acini. 8x10^6 alveolar sacs.

Each alveolus has the capillary endothelium, supporting tissue, interstitial cells and then type 1 pneumocyte (95%, site of gas exchange) and type II pneumocytes (can become type I to replace, secrete surfactant)

Gas Exchange

There are three components to the exchange:

1. Ventilation: this process is dependent upon the volume entering, the distribution, composition. Know that the TLC is 6L, Tidal volume is 500ml, Residual volume is 1.5L. Residual volume and functional reserve capacity allow for continual gas exchange throughout the respiratory cycle, buffer the changes in PO2 during respiration and prevent collapse of the lungs. Spirometers can calculate some lung volumes. TLC, RV, FRC are calculated by gas dilution techniques (helium or N2 washout) or plethysmography (measures all air even trapped air in diseased lungs).
   Hyperventilation=increased alveolar ventilation= PaCO2<35. Hypoventilation is the opposite and PaCO2>45. Realize the apex (nondependent region) has less ventilation and the base (gravity dependent region) has the best ventilation due to increased hydrostatic pressure from to gravity.
2. Pulmonary diffusion: diffusion is comprised of membrane diffusion (from

Equations:

capillary to plasma to cytoplasm) and chemical reaction with Hb. This membrane is comprised of alveolar epithelium, interstitial space, pulmonary capillary endothelium that all together is less than 5microns. Fick's law states the rate of a gas V=(AreaxPressureXDiffusion coefficient)/Thickness. Increased thickness (interstitial/alveolar edema, fibrosis) decreases in area (emphysema, tumor, low CO, low blood volume, poor ventilation/perfusion match) all decrease the rate of diffusion. Increased area (exercise induced increases in performance and alveolar development) will show increased rates of diffusion.

Aside from the composition of the membrane itself, the partial pressure and characteristics of the gases themselves will also impact the rate of diffusion. High altitudes, hypoventilation will decrease the O2 partial pressure gradient while increased F_IO2 inhalation will increase the gradient and rates of diffusion. The Fick's equation can be rearranged such that the solubility/density(a constant) equals a diffusion coefficient. This rearrangement shows that CO2 has 20x the diffusability of O2. However, the partial pressure gradient of O2 makes it that the equilibration time for O2 and CO2 are both nearly identical (1/4 of a second). Normal capillaries with a resting CO will have a single RBC in the capillary for a total of ¾ of a second such that for ½ of a second, the RBC is at a steady state and no gas is diffused (this time is called the capillary reserve and is necessary especially in the case of specific disease states.).

Equilibrium time=.25sec and capillary transit time is .75sec at rest and .25 during exercise. Clinically the pulmonary diffusion is measured by rearranging Fick's equation to generate a Diffusion Capacity variable D_L=Flow of a gas/change in pressure. Using this with a small dose of CO, the physician can measure the nature of the membrane (CO diffusion is purely limited by the diffusion properties of the membrane… not blood flow). O2 and N20 are "perfusion limited" since their uptake depends on not only the membrane but the rate of blood flow. Severe impairment of the membrane O2 becomes more like CO and is considered diffusion limited. Flow of CO/P_ACO can give an estimate of diffusing capacity of the lung.

Once in the blood, O2 can travel in the plasma, the cytoplasm or with the Hb. Dissolved blood O2 depends on Henry's law with the pressure x solubility coefficient=Dissolved gas amount. Usually given as mLO2/dL of blood (volume%). However, most of the O2 binds to heme group in hemoglobin. Oxygen will bind to the 4 subunits (2alpha2beta) in sequential reactions. As each O2 binds, the affinity for more O2 has a 500 fold increase generating a sigmoidal curve. 100mmHg O2 saturation is 97.5%, venous blood 40mmHg saturation is 75%. The amount of O2 depends on the concentration of Hbx1.39(the absolute binding capacity of O2)x% O2saturation. Total O2 content therefore is the dissolved O2+HbO2. Delivery to tissues requires the Bohr Effect which states that O2 has a higher affinity for Hb at higher O2 concentrations and lower affinity at lower concentrations. This affinity can be shifted depending on local metabolic factors. Increased H+, CO2, temp, 2/3BPG can all shift the binding curve to the right such that the P_{50} of Hb is higher and O2 is more likely to be released from Hb. This will help tissues that are metabolically active due to exercise or infection.

3. <u>Circulation:</u> the pulmonary system has: lower pressures, increased flow, lower resistance due to higher distensibility of vasculature that is thin with less smooth muscle cells. Pulmonary blood flow is equal to the CO of systemic blood flow since they are two pumps in series. CO=PBF=SVxHR. PBF=O2consumption/O2 extraction… O2 consumption can be calculated by finding the VO2flow (Fick's law). Thermodilation techniques can also be used to calculate PBF. Realize that pulmonary vessels are more distensible AND compressible. This lets the lungs act like

a blood reservoir with a shift in blood volume of up to 400ml between standing and lying down. The majority of vascular resistance is mediated by Passive measures.

a. Passive control: Increased BP/flow/PAP will stretch the vessels to decrease resistance. Increases in lung volume above FRC will increase resistance due to increased stretching of the alveolar capillaries which will lengthen them and decrease their diameter. Decreases in lung volume below FRC (forceful expiration) will increase the extra alveolar resistance due to a positive pleural pressure being generated by the expiratory intercostals. Positive lung ventilation forces air into the capillaries to increase the alveolar pressure and increase resistance by compression of the capillary bed. Lastly, gravity will cause differential blood pooling in three specific zones where the first zone represents $P_A > P_a > P_v$, then $P_a > P_A > P_v$ and finally the lowest zone with the greatest influence due to gravity will have $P_A > P_v > P_A$ and the lowest resistance (greatest tissue perfusion)

b. Active control: Direct vasoconstriction (Low P_AO2, increased CO2, drop in Ph, alpha adrenergic stimulation, ATII, TXA2, Histamine. Vasodilation by way of NO, Antiendothelin, AchM3, B2 agonists, bradykinin or PGI2/E1

Hypoxia

Hypoxia is a state of low O2 concentration at the tissue level. It can be caused by **4** things **HASH**

1. Hypoxemia: is a state of low PaO2 with low levels of dissolved O2
2. Anemia: low Hb content. There is either low concentration of Hb or the Hb is impaired. In the first case the % saturation and dissolved are normal while the total is low. Anemic hypoxia due to low % O2 saturation, the Hb is impaired such that they can't be loaded with O2
    a. Methemoglobinemia: congenital, Nitrite poisoning, Toxic Rx to drugs
    b. CO: CO has 240x the binding affinity for Hb… additionally once it binds, it increases the binding affinity for the O2 already bound and also impairs oxidative phosphorylation (histotoxic hypoxia)
3. Stagnant: hypoperfusion…there is plenty of O2 but it can't get to the tissue causing local ischemia or systemic hypoxia if it is the result of low cardiac output. Increased O2 extraction to compensate
4. Histotoxic: impaired O2 utilization (can't extract the O2). All levels read as normal but there is a failure at the cellular level to utilize O2
    a. Cyanide: binds cytochrome oxidase
    b. CO: inhib of oxphos
    c. Primary mito resp chain disease

Edema: this is a progressive disease from increased interstitial exudate to edema to alveolar edema/exudate. Pulmonary Capillary Wedge Pressure can be used to determine the extent of the edema and also evaluate LV function (good for CHF)

II Diseases (Obstructive, Restrictive, Atelectasis, Acute, Vascular complications, Infection)

Obstructive Pulmonary diseases

A group of diseases with increased resistance to air flow (partial or complete) anywhere in the respiratory tree. PT present with dyspnea, chronic/recurrent obstruction, limitations to flow during forced expiration. NOTE: COPD is emphysema and bronchitis.

Bronchial diseases: Chronic bronchitis (irreversible), Asthma (reversible), Bronchiectasis

Acinus disease: emphysema (irreversible)

Bronchiole: small airway disease, bronchiolitis (pre chronic bronchitis)

1. Chronic bronchitis: **Mucus gland hyperplasia/secretion**. Persistent productive cough for 3months per year and 2 consecutive years w/o any other identifiable cause. 90% of cases due to cigarettes; microbial infection can trigger acute exacerbations;50yo male, "Blue Bloater". The **Reid index** is a ratio of the measured width of submucosal glands to the full width of the tissue from the BM to the cartilage. There is a variable degree of inflammation/fibrosis (**bronchiolitis Obliterans**) and squamous metaplasia/dysplasia. **SX** initial cough->dyspnea->mild cyanosis->Cor Pulmonale. Commonly have infections, repeated insufficiency, normal elastic recoil and Cor Pulmonale BIG HEART.
    a. Bronchiolitis**:** is often an early manifestation of chronic bronchitis. Small bronchi/bronchioles are inflamed with goblet metaplasia and fibrosis
2. Emphysema: **Airspace enlargement WITH destruction**. The enlargement is permanent and the result of tissue damage. There is a noticeable lack of significant interstitial fibrosis. More common/severe in males, clearly linked to smoking and the first signs are ventilation defects decades before emphysema. Alpha1-Antitrypsin (a1-AT) is a protease inhibitor produced in the liver that inhibits elastase (produced by neutrophils). **SX** these appear when 1/3 parenchyma affected. "Pink Puffer" Dry cough, weight loss, marked inflation of the lung, resp acidosis, pneumothorax and maybe RCHF. Severe dyspnea, occasional infection, terminal (when insufficiency or Cor Pulmonale), destruction of elastic fibers, SMALL HEART due to hyperinflation.
    a. Centriacinar (Centrilobular): upper lobe, often seen with bronchitis/smoking, central parts are affected while the distal portions are normal… emphysematous and normal areas can be seen in the same acinus or lobule. PATHO: smoke particles impact small bronchi, neutrophils and macro invade and secrete elastase while the a1-AT is impaired due to free oxygen radicals in the tobacco and the poor perfusion of the upper lobe.
    b. Panacinar (Panlobular): lower lobe, a1-AT deficiency (PiZZ instead of PiMM), both the central and distal equally affected. PATHO: deficiency throughout the acinus and neutrophils normally in the lower lobe with more perfusion so increased damage here when neutrophils are activated.

c. Distal acinar (paraseptal): upper lobe, predominantly distal portion near the pleura of the lung. Associated with spontaneous pneumothorax in young adults. Typically young males with severe dyspnea (pleural irritation caused by O2 feels like needles/sharp)

3. Overinflation: enlarged spaces without destruction of the tissue. Compensatory overinflation is caused by response to a lobectomy/unilateral pneumonectomy. Obstructive is due to ball-valve action due to a tumor/foreign body or a congenital deformity (hypoplasia of bronchial cartilage).
4. Asthma: **SMC hyperplasia, excessive mucous, wheezing, Chronic/hyperactive**. This is chronic relapsing condition due to a hyper-reactive tracheobronchial epithelium. There are episodic bronchoconstriction events due to extrinsic (immune issue) or intrinsic (non-immune) causes. 10% of kids/5% adults. The disease is becoming more prominent and seen often before the age of 10. Bronchoconstrictors: Leuko C4,D4,E4, AH, Histamine and Prostaglandins. Platelets aggregate, release histamine and serotonin and act as mediators. Major basic protein of eosinophils cause epithelial damage. **SX** thicken BM, edema/inflammatory infiltrate/ eosinophils, ↑ submucosal gland, ↑goblet, ↑SMC.
   a. Extrinsic**:** often atopic (allergy hypersensitivity type I), occupational or Aspergillosis. Familial history and begins in childhood.
      i. **ADAM-33:** from lung fibroblast/lung SMC, polymorphism increases its expression to stim proliferation
      ii. **IL4:** gene variants are associated with atopy
      iii. **YKL-40:** chitinase increases TH2 inflammation and is a marker of severity.
   b. Intrinsic: drug induced (aspirin), viral infections, irritants, stress, cold, exercise. No history and in adults during viral infection (viral induced inflammation lowers the threshold of the subepithelial vagal receptors to irritants). **SX** Triad: **Recurrent rhinitis, nasal polyps, asthma (maybe urticarial).** Inhib of COX for arachidonic acid but not leukotrienes.

NOTE: Charcot-Leydens are major basic protein from eosinophils. Curshmann spirals are mucus with epithelial cells attached. Status asthmaticus is severe constriction for days that could lead to death

5. Bronchiectasis: **Airway dilation with scarring and purulent sputum; bilateral, lower lobe (unless due to obstruction).** Chronic necrotizing infections lead to irreversible dilation from the destruction of muscle and elastic tissue. Dilation must be permanent and this leads to the predisposition to develop abscesses. Caused by congenital (CF, immunodef, Karganoner, "sick cilia disease"), post infection (pneumo from staph/pseudomonas), RA/SLE/IBS/Post transplant due to immune suppression. **SX** obstruction->infection->inflammation->necrosis/fibrosis->dilation. Most severe dilation in the distal bronchi (4x normal dilation). The transected bronchi look like cysts with fowl smelling, mucopurulent material. Complications: Cor Pulmonale, metastatic brain abscess, amyloidosis.
   a. Active: acute/chronic inflammatory exudate, desquamation, necrosis, squamous metaplasia, abscess
   b. Chronic: fibrosis, subtotal/total obliteration of the lumen.
6. Cystic Fibrosis: **Autosomal recessive 7q31.2 CFTR** most common lethal genetic disease in Caucasians (very rare in African Americans/Asians. 1 in 3200 live births and 2-4% are carriers. There is primary defect in the CFTR of epithelial chloride transport in exocrine/ecrine glands. **SX: Triad** severe recurrent infections in the resp, steatorrhea, azospermia. Lungs have thick plugs, staph/pseudomonas, bronchitis, bronchiectasis, abscess. Pancreas with progressive fibrosis leading to diabetes, steatorrhea due to plugged ducts. Liver due to plugged bile ducts with 5%

progressing to cirrhosis. Sweat glands fail to reabsorb Na from the lumen of accrine sweat glands causing salty sweat. Epididymis and vas: azospermia or absence of structures. **This is obstructive lung disease not restrictive.**

- **a.** Class I: defective synth causes a lack of CFTR at the apical surface of cells
- **b.** Class II: abnormal protein processing
- **c.** Class III: defective regulation (nonfunctional but normal levels)
- **d.** Class IV: Decreased activity (only partially functional)
- **e.** Class V:low numbers of perfectly functional regulator
- **f.** Class VI: altered reg of separate ion channels that affect the role of CFTR

Diffuse interstitial diseases… a subset of Restrictive lung disease

Restrictive lung diseases: reduced expansion of the lung, reduced total lung capacity while the expiratory flow rate is relatively intact (as opposed to obstructive). These diseases present as chest wall disorders (neuro, obesity, kyphoscoliosis, pleural disease), acute interstitial/infiltrative disease (ARDS), chronic diffuse diseases. **Injury-> Alveolitis->Cellular/CT alterations->Fibrosis->Honeycomb lung**

Diffuse and chronic involvement of the pulmonary CT is often bilateral (and alveolar interstitium); dyspnea, tachypnea, end inspiratory crackles without wheezes; small nodules, lines/ground glass, honeycomb seen on x-ray; progression to Cor Pulmonale. This is most often caused by environmental agents>Sarcoidosis>idiopathic>collagen vascular disease.

Alveolitis is the earliest manifestation and the base pathogenesis of all these diseases regardless of the cause. This characterized by increased inflammation and immune cells in the alveolar wall and space causing distortion and release of chemokines that injure the parenchymal cells.

A. Fibrosing disease:

1. Idiopathic pulmonary fibrosis: **Lung scarring of unknown origin**. Diagnosis of exclusion; pattern of patchy interstitial fibrosis with continual repetitive cycles of injury and then healing. Type II pneumocytes try to replace damaged Type I but they are more cuboidal and fibroblasts proliferate. It is insidious, 40-70 year olds with survival of <3yrs. Microscopic exam shows thick septa.
2. Cryptogenic Organizing Pneumonia (bronchitis organizing pneumonia): unknown etiology or secondary to infections; acute-subacute with fever, cough, dyspnea; polyploidy plugs of loose fibrous tissue in the bronchi and alveoli. Supportive therapy is recommended with a good prognosis.
3. Pneumoconioses: **organic/inorganic dust inhalation**; slow, insidious, usually occupational or urban areas. 4 factors amount(concentration, duration, effectiveness of clearing mechanisms) size/shape(most dangerous are 1-5microns and brittle) particle solubility(smaller particles have better solubility and cause acute injury while larger cause chronic injury and fibrosis) additional (depending on the nature of the irritant)

a. Coal workers Pneumoconiosis CWP: starts as asymptomatic anthracosis (carbon pigment engulfed by macrophages accumulate in the CT along pulmonary lymphatics and in LN), simple CWP (**coal macules and nodules** contain carbon, mostly in upper lobes, assoc with centrilobular emphysema) complicated CWP(progressive, multiple irregular black scar i.e. **progressive massive fibrosis PMF**). The CWP has increased risk of TB, chronic bronchitis, emphysema but not cancer.

b. Caplan Syndrome: CWP with RA. The nodular lesions are similar to RA nodules in lung (fibroblasts, macro, collagen surround central necrotizing regions).

c. Silicosis: most prevalent occupational disease seen in sandblasters/miners and is slowly progressive with nodular fibrosis. Due to crystalline forms (quartz). Amorphous forms like talc not as big a risk. Macro release fibrogenic cytokines TNF, IL-1. Tiny collagenous nodules in the upper lungs will enlarge and then coalesce to form visible collagenous scars (**PMF**). LN become calcified and seen as "egg shell calcifications". Microscopic analysis shows hyalinized, rounded, collagenous nodules with concentric layers housing silica. Fine nodularity (eggshell) seen on x-ray, with fairly normal pulmonary function tests. Increased risk of TB since silica interferes with macrophages ability to kill the bug.

d. Asbestos: crystalline hydrated silicates forming fibers that are found in the lower lobes of the lungs and subpleurally. **Serpentine** is less pathogenic and more common while **amphibole** is less soluble, brittle and delivered deep into lungs (cause mesothelioma). Progression is diffuse asbestosis->localized fibrous pleural plaque (assymp)->pleural effusion->cancer. The fiber is golden brown beaded rod with a clear center (iron contained proteinaceous material on the crystal). **NOTE: ferruginous body** is an inorganic fiver other than asbestos. The risk for cancer is 55x if asbestos AND a smoker (the carcinogens are collected by the fibers). Slow course, sx appear years later.

Drug	Pulmonary Disease
Bleomycin	Pneumonia and fibrosis
Methotrexate	Hypersensitivity pneumonitis
Amiodarone	Pneumonitis and fibrosis
Nitrofurantoin	Hypersinsitivity pneumonitis
Aspirin	Bronchospasm
β-Antagonists	Bronchospasm

4. Complications of therapy: several classes of drugs cause acute or chronic damage

B. Granulomatous diseases:

1. Sarcoidosis: **Noncaseating granulomas** diagnosis of exclusion, multisystem disease (unknown cause) with noncaseating granulomas. Typically seen in early to middle aged females (AfricanAmer?). It could be caused by disordered immune regulation (tcell deregulation). **SX** granulomas in diffuse interstitial lung involvement, bilateral hilar LN, tonsil/spleen/BM/Skin/Eye/Salivary/Muscle… sometimes the heart, kidney, CNS. Completely variable symptoms but need **Cough, Erythema nodosum, Dyspnea** and can have neuro manifestations. Lab results show High Ca, ACE, low CD4. The outcome is chronic-remitting and spontaneous remission or remission with steroids. **65-70% full recovery, 20% w/ permanent lung/visual problems, 10-15% die due to progressive fibrosis leading to Cor Pulmonale.**
2. Hypersensitivity Pneumonitis: **Hypersensitivity III and IV** Immunologically mediated, alveoli primarily affected… due to intense (often prolonged) exposure and inhalation of organic dusts. TX requires removal from environment. It can present as Acute (4-6hrs after exposure causes fever, dyspnea, cough) or chronic.

C. Smoking related injury:

1. Desquamative Interstitial Pneumonitis: large collections of macrophages in the air spaces (it's a misnomer). The disease has minimal fibrosis, mostly middle aged males with an insidious onset of dyspnea and cough. Good prognosis with steroids and cessation of smoking.

Lung diseases: random diseases that don't fit anywhere else

1. Pulmonary Eosinophilia: acute, simple, tropical (microfilaria), allergies, churg strauss… these all have eosinophilia in the interstitium of the lungs with variable disease outcomes.
2. Pulmonary Alveolar Proteinosis: bilateral opacification on x-ray; acellular surfactant in alveoli and bronchioles that can't be cleared due to macrophage impairment. **Acquired, secondary, congenital** all have PT coughing up "gelatinous mixture". **GM-CSF** is usually the offending gene. Without the gene, macrophages do not proliferate as they should.
3. Atelectasis: incomplete expansion or collapse of a previously inflated lung (not due to trauma). It is generally reversible unless scarring has occurred.
    a. Obstruction: complete obstruction of the airway (not partial like we see in obstructive diseases) due to secretion plugs or aspiration (tumors will usually produce incomplete obstruction and localized emphysema). **Mediastinal shift towards the lung**
    b. Compression: fluid/blood/tumor/clot/air all fill the pleural space to compresses the lung, or due to an abnormally elevated diaphragm pressing the lung (due to peritonitis, subdiaphragmatic abscess). **Mediastinal shift away from lung**
    c. Contraction: local or general fibrosis in the lung or pleura prevent lung expansion
4. Acute lung injury: this is caused by pulmonary edema or ARDS
    a. Pulmonary edema: hemodynamic (increased hydrostatic pressure of CHF/volume overload or decreased oncotic pressure) microvascular injury (infection, gas, drugs, liquid aspiration, shock, **Oxygen toxicity, Transfusion injury**) undetermined (high altitude or neurogenic). The lungs are heavy, wet, frothy with some blood (worst in the lower lobes) with changes leading to impaired pulmonary function(interstitial) and an increased risk of infection(alveolar with eosinophilic precipitate). **Brown induration** is a the result of long standing chronic passive congestion with increased heart failure cells and interstitial fibrosis.
    b. ARDS: **Alveolar flooding** RAPID onset, cyanosis, SEVERE hypoxemia that does not respond to O2 since the lung is damaged. Most commonly caused by: **Sepsis, infection, gastric aspiration, head trauma.** Uremia is also a common cause. Diffuse damage to the alveolar capillary walls (usually the endothelium) causes an increased permeability that lest fibrin leak into the alveoli (comparable to crescentic necrosis). Damage to Type II with surfactant abnormalities. DAD (diffuse alveolar damage) with interstitial then alveolar edema. Hyaline membranes form in the alveoli (full of fibrin, lipids, necrotic epithelial cells). IF you survive…. Organizing stage shows organization of fibrin exudate, hyperplasia of Type II, fibrosis, honey-comb lung
5. Diseases of vascular origin: These are a wide range of clinical presentations
    a. PE: usually DVT in the legs; most are clinically silent because sooo small. Some have hemorrhage, transient cough or pain. **10% infarct (coexisting lung/heart disease), 30% develop a second emboli.** Acute right heart failure and sudden death (if a large clot with saddle

embolism) and PT will show electromechanical dissociation (Pulsus paridoxicus). Smaller chronic clots can lead to pulmonary hypertension. NOTE: emboli have **Lines of Zahn** that are fibrin and platelets surrounding a core of RBC. **Fat** fractured long bone; **Air** due to trauma, frothy blood seen in RV and PA; **Carcinomatosis** seen with breast, stomach, lung emboli that disseminate (PT will die before an issue); **Septic** due to bacteria or fungi fragments with neutrophils and can become an abscess; **BM** usually seen from CPR and not a problem; **Amniotic** seen at the time of delivery, it is serious, causes shock, and diffuse alveolar damage in large amounts; **Starch/talc** think drug users with little granulomas that aren't fatal. **DIAGNOSIS** requires a spiral computed tomographic angiography and a d-dimer

b. Infarct: usually wedge shaped, at the periphery, emboli at the apex and coagulative necrosis (recent infarct), liquifactive necrosis (brain), scaring with hemosiderin macrophages (old infarct)
c. Hypertension:**BMPR2** Primary (idiopathic) is mostly early-middle aged women with **dyspnea, fatigue, +/- angina**. PT will have Cor Pulmonale that is fatal in 2-5 years. This is TGF-Beta mutation in a gene that normally inhibits proliferation of SMC. Atheromatous plaques will develop in the main arteries, medial hypertrophy/intimal prolif with fibrosis in arterioles, **Plexogenic pulmonary arteriopathy** in the lungs with plexiform lesions that are capillary tuft formations (severe and irreversible). This looks like onion skinning except not in the peripheral tissues it's in the lungs.
d. Hemorrhage: **Goodpasture:** diffuse infiltrates with necrotizing hemorrhagic interstitial pneumonitis and rapid Glomerulonephritis. Mostly seen in males in the teens and twenties. Uremia is a cause of death. Viral, smoking and hydrocarbons are possible cofactors for the disease. **Idiopathic Pulmonary Hemosiderosis:** cough, anemia, weight loss, hemoptysis (kids), degen/hyperplasia of alveolar epithelial cells. Capillary dilatation and pulmonary fibrosis occurs with the presence of "heart failure cells". **NOTE: Wegener, Lupus, Hypersensitivity angitis also have hemoptysis.**

III Pulmonary Infection

Most frequent infection in the human body and major cause of immediate death **(Pneumo, Abscess, TB)**. Most upper respiratory infections are caused by viruses.

The normal defenses include:

- Nasal clearance by sneezing/blowing or cilia (posteriorly) remove debris to the back of the nasal passage to be swallowed
- The epiglottis, coughing, cilia all help prevent aspiration in the tracheobronchial regions
- The remaining debris is removed from the acinus by way of macrophages.

Pathogenesis:

- **Entry:** respiration, aspiration, hematogenous spread, nosocomial
- **Impairment of defense:** loss of cough reflex, damaged mucociliary apparatus, interference with macrophage function
- **Congestion/Edema/increased secretions**
- **Lowered immunity:** immunodef/suppressed, chronic diseases, leukopenia, virulence of infection

Pneumonia: Acute inflammation of the lung parenchyma. Sputum stain/culture, rapid urine test (legionella), x-ray, CBC, blood culture, blood gases. <10% die due to meningitis, empyema, endocarditis, pericarditis (usually a predisposing condition like chronic alcoholism). Abscesses are local suppurative necrosis (Strep pneumo 3 or Klebsiella)

1. **Lobar pneumonia:** virulence and vulnerability determine the degree of involvement. Extensive exudation in the lung is made possible by the **pores of Kohn.** There is NO alveolar injury. Strep pneumo is the number one cause (type 3 is the worst), and also kleb pneumo (currant jelly sputum). Pseudomonas and Proteus are rarer. Stages: Congestion (4-12hrs), red hepatization (12-48hrs), gray hepatization (3-8days), resolution (7-11days)
2. **Bronchopneumonia:** Staph, strep, pseudomonas, H influenza, Klebsiella; forms 3-4cm lesions, patchy, consolidated, multilobular, bilateral and basal. Suppurative lesions with neutrophils and may have necrosis; PT can have fibrinosuppurative pleuritis, hypoxia, and cyanosis.
3. **Aspiration pneumonia:** could be foreign body, food, vomit, secretions; partially chemical pneumonia and partially bacterial. Often it is a group of necrotizing, aerobic, fulminant microbes.
4. **Atypical Pneumonia:** community acquired (usually mycoplasma) with acute fever, patchy inflammation of the alveolar septa and interstitium WITHOUT exudate. There is infrequently pleural involvement, both lobes may or may not be involved and the lungs are red-blue with congestion and subcrepitance. (Influenza, RSV, Adenovirus, SARS, CMV, Herpes, Chlamydia, Coxiella burnetti). DAD is present on microscopic exam. SARS is 2-10 day incubation, malaise, myalgia, fever, diffuse damage with multinucleated giants. EM shows virus in pneumocytes.

5. **Immunocompromised Pneumonia:** common, serious, more than one agent. Diffuse: CMV, Pneumocystis, Drug RX Focal: gram neg, staph, aspergilosis, candida

Fungal lung infections: dependent up on the nature of the fungus, host status and the geography.

1. **Histoplasmosis:** dust with bird/bat droppings is inhaled. Primary Respiratory infection endemic to the ohio river valley
2. **Blastomycoses:** Primary pathogen mostly south eastern states with pulmonary, disseminated and cutaneous infection forms
3. **Coccidoidomycosis:** primary
4. **Apsergillus:** found everywhere and indicative of underlying Neutrophil def
5. **Cryptococcus:** Opportunistic in tcell def PT
6. **Mucormycosis:** Opportunistic with necrosis of nasal mucosa in diabetics

Abscesses in the lung: very rare and is characterized by necrosis of lung tissue by bacteria. Abscess is caused by aspiration, antecedent primary bacterial infection (Staph, Kleb, Strep pneumo 3), septic emboli, **Neoplasm (10-15%)**, hematogenous, iatrogenic. Gross appearance is a cavity filled with suppurative debris; Microscopic appearance is **suppurative destruction of parenchyma within the central area of cavitation.** The patient has fever, productive cough copious sputum that is foul/purulent/sanguineous; c**lubbing of the fingers** and often secondary to cancer. Most often ABX can treat. May have brain abscess, meningitis or extension to the pleural cavity.

TB: Primary TB, Secondary TB, Progressive pulmonary TB (Cavitary, Miliary, Bronchopneumonia, Pleurisy). Mycobacterium bovis/africanum/caprae/micoti make up the TB complex. MOTT (Mycobacterium other than TB) are comprised of leprae, avium/intracellulare, marinum, ulcerans. MDRTb is a new resistant form.

Aerosolized particle inhaled into the alveoli or ingested in unpasteurized milk. Dust cells take up the bacteria and kill. The PT is officially exposed but not infected. If the bacteria replicates in the alveolar space, it does so for a few weeks and spreads to the hilar lymph nodes where granulomas and Ghon complexes are formed. Tcell response is now generated making the PT PPD (+) after 3-9wks. Most patients will stop here are considered LTBI (Latent TB Infection) of which 10-15% will reactivate. Some of these macrophages can also disseminate from the ghon complexes to form disseminated TB.

1. Primary: Infection with TB without previous exposure (Ghon complex, Asymptomatic, Progressive to Miliary)
2. Secondary: Reactivation
3. Cavitary Fibrocaseous: Erosion of a lesion into a bronchiole with hemoptysis
4. Miliary: Infection gains access to bloodstream/lymphatics to spread (pulmonary spread or systemic spread)
5. Bronchopneumoniae: an aggressive pneumonia without granulomas.